The Efficacy of Amphetamines for 64 Hours of Sustained Operations

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Introduction

Dextroamphetamine sulfate (Dexedrine®) is a powerful central nervous system (CNS) stimulant that improves alertness and postpones the need for sleep. In aviation, where a high degree of alertness is essential during long flights, dextroamphetamine can counteract the decreased vigilance and attention, slowed reaction time, negative psychological mood, and sometimes perceptual disturbances associated with severe fatigue.

Countermeasures other than dextroamphetamine have been tested to overcome these problems, but the most popular strategy, that of emphasizing proper work/rest management, is almost impossible to successfully implement due to the unpredictability of combat operations. Other potential measures such as brief periods of exercise only temporarily reduce the negative impact of sleep loss[12, 8, 1] while exposure to cold air or noise is virtually ineffective or, in the case of loud music, actually deleterious.[9] Improving the physical fitness of personnel likewise does little to reduce the impact of sleep loss.[2]

Stimulants are more reliable for maintaining performance, especially in aviation operations where the passive nature of piloting an aircraft tends to enhance sleepiness in fatigued individuals. Of the stimulants available, dextroamphetamine (Dexedrine®) ranks favorably because its actions are known and its effectiveness has been fairly well established. Methamphetamine is similarly useful,[22, 23] but may pose a higher abuse potential. Caffeine, although easy to acquire and socially acceptable, is less effective.[18] Modafinil, a new psychostimulant, may eventually prove useful,[11] but modafinil appears to be only mildly or moderately effective in comparison to dextroamphetamine for reducing excessive sleepiness.[15]

Although the short-term efficacy of dextro-amphetamine is reasonably clear,[7, 6, 4] longer-term studies are necessary to explore whether Dexedrine can extend performance for more lengthy periods without creating problems associated with tolerance or side effects. This study sought to extend our understanding of the usefulness of dextroamphetamine beyond 40-hour periods of sustained wakefulness those requiring a total of 64 hours without sleep.

Methods

Subjects

Six UH-60 helicopter pilots resided in the U.S. Army Aeromedical Research Laboratory (USAARL) for a period of 10 days each. The mean age was 33.3 years (range was 27-40), and the mean total flight time was 1245 hours (range was 200-2700).

Apparatus

Two gelatin capsules were administered at each dose time. Each active capsule contained one 5-mg tablet of Dexedrine, and each placebo capsule contained lactose powder. *Flights* were conducted in a specially-instrumented UH-60 simulator with computer-generated visuals (set for daytime flight) and a six-degree-of-freedom motion base. *Waking electroencephalograms (EEGs)* were recorded from F_z, C_z, and P_z on a Cadwell Spectrum 32. The low and high filters were set at 0.53 and 20 Hz, respectively, and the 60 Hz notch filter was used. *Mood* was assessed with the Profile of Mood States (POMS),[14] a 65-item test which measures affect on 1) tension-anxiety, 2) depression-dejection, 3) anger-hostility, 4) vigor-activity, 5) fatigue-inertia, and 6) confusion-bewilderment. *Sleep architecture* was examined using a Nihon Kohden electroencephalograph. EEG data were recorded from C_3, C_4, O_1, and O_2 (referenced to contralateral mastoids). Electromyogram (EMG) data were recorded from under the chin. Electrooculogram (EOG) data were recorded from the outer canthus of left and right eyes (referenced to A_1). Time constants and high filter settings were: 0.3 sec. and 35 Hz for EEG, 5.0 sec. and 10 Hz for EOG, and 0.003 and 120 Hz for EMG.

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Procedure

Training sessions were conducted at 0900, 1300, and 1700 on Tuesday-1 (training day). On Wednesday-1 (control), Saturday-1 (recovery), and Sunday-2 (control), there were testing sessions at these times as well. On Thursday-1 and Friday-1 (the deprivation days in the first cycle), and on Monday-2 and Tuesday-2 (the deprivation days in the second cycle), testing occurred at 0100, 0500, 0900, 1300, and 1700. On these days, drug or placebo doses were administered at 0000, 0400, and 0800. The study was double blind and counterbalanced.

Flight performance

Upper-airwork maneuvers were flown both with the automatic trim system engaged (the normal mode in the UH-60) and with the trim system off (to increase pilot workload). During maneuvers, subjects were required to maintain specific flight parameters. Scores ranging from 0-100 (with 100 reflecting near perfect accuracy) were calculated based upon the extent to which subjects deviated from target values (see table 1). Individual parameter scores were averaged to produce one composite flight score for each iteration of each maneuver.

Table 1. Scoring bands for flight performance

	Maximum deviations for scores of:					
Measure (units)	100	80	60	40	20	0
Heading (degrees)	1.0	2.0	4.0	8.0	16.0 >	16.0
Altitude (feet)	8.8	17.5	35.0	70.0	140.0 >	140.0
Airspeed (knots)	1.3	2.5	5.0	10.0	20.0 >	20.0
Slip (ball widths)	0.0	0.1	0.2	0.4	0.8 >	0.8
Roll (degrees)	0.8	1.5	3.0	6.0	12.0 >	12.0
Vert. Speed (feet/m)	10.0	20.0	40.0	80.0	160.0 >	160.0
Turn Rate (degrees/s)	0.3	0.5	1.0	2.0	4.0 >	4.0

EEG evaluations

In each EEG session (15 minutes postflight), data were collected under eyes open and eyes closed. There were three iterations of eyes open/eyes closed during each session. Absolute power values were calculated for each iteration. The activity bands were: delta (1.5-3.0 Hz), theta (3.0-8.0 Hz), alpha (8.0-13.0 Hz), and beta (13.0-20.0 Hz).

POMS

The POMS was given 45 minutes after the EEG. Subjects indicated on the test form how well each of 65 mood adjectives described the way he/she was presently feeling.

Polysomnography

On each of the nights when sleep was allowed, subjects slept for approximately 8 hours while electrophysiological data (EEG, EOG, and EMG) were recorded. Standard scoring[21] yielded sleep time, minutes until the first minute of stage 2 (sleep onset), minutes from sleep onset to the first 2 minutes of rapid-eye-movement sleep (REM), the percentage of time in stages 1-4 and REM, the minutes of movement, and the percentage of time awake after sleep onset.

Results

Flight performance data

Flight performance scores under placebo versus Dexedrine during 3 baseline flights (at 0900, 1300, and 1700) and 10 deprivation flights (0100, 0500, 0900, 1300, and 1700 on deprivation days 1 and 2) were analyzed with a 3-way analysis of variance for drug, session, and iteration.

Straight and levels (SLs). A drug-by-session interaction was due to an absence of differences at baseline or the 0100 flight on the first deprivation day, which was followed by impairments under placebo relative to Dexedrine at 0500 and 1300 on day 1, and at 0100, 500, 0900, and 1300 on day 2 (see figure 1). A drug main effect was due to lower scores under placebo than Dexedrine (74.0 versus 80.1).

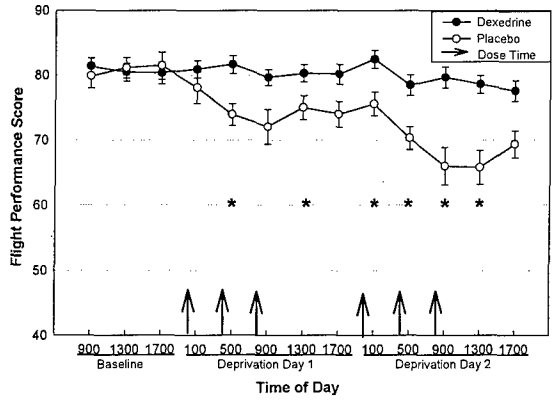

Figure 1. Straight and level flight performance

Climbs. Scores revealed a drug-by-session interaction due to decrements under placebo at 0900 and 1700 on the first deprivation day ($p<.05$) and a tendency at 0500 on the second deprivation day ($p=.0569$). There

were no effects at other times (see figure 2). A main effect on the drug factor was due to poorer performance under placebo than Dexedrine (61.6 versus 67.1).

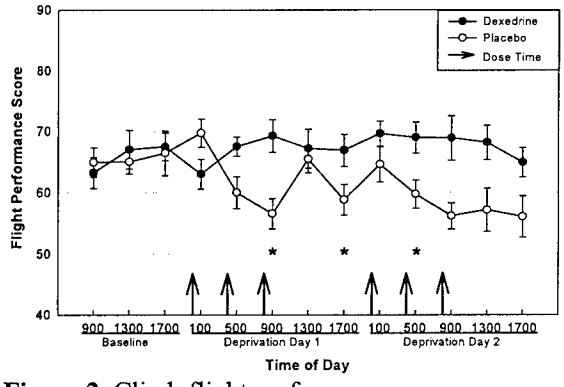

Figure 2. Climb flight performance

Descents. A drug-by-session interaction occurred because there were no differences at baseline, but performance under placebo was poorer compared to Dexedrine at 0500, 0900, 1300, and 1700 on the first deprivation day, and at 0500, 0900, and 1300 on the second day ($p \leq .05$). Performance tended to be poorer ($p = .0563$) at 1700 as well (see figure 3). A drug main effect was due to poorer performance under placebo than Dexedrine (48.8 versus 56.2).

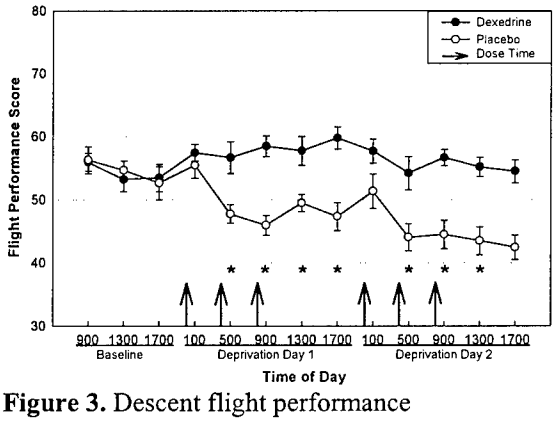

Figure 3. Descent flight performance

Left standard-rate turns. A drug-by-session interaction resulted from the absence of drug differences during baseline or at 0100, 0500, or 0900 on the first deprivation day, whereas flight control was less accurate under placebo than Dexedrine at 1300 on the first deprivation day and at 0900, 1300, and 1700 on the second day ($p < .05$). See figure 4.

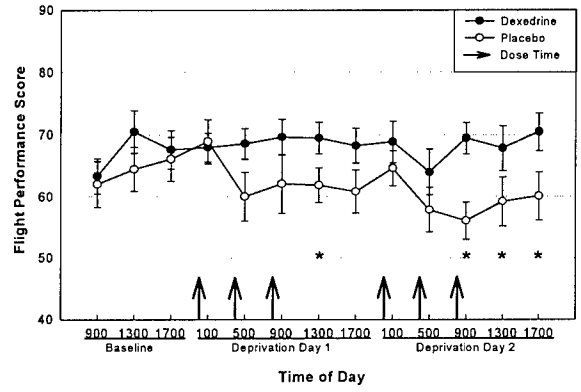

Figure 4. Left standard-rate turn performance

Right standard-rate turns. A drug-by-session interaction occurred because of the absence of differences at the predrug sessions and the first postdrug session, but poorer performance under placebo than Dexedrine at 0500 and 1700 on the first deprivation day and at 0100, 0900, and 1300 on the second day (see figure 5). A main effect was found on the drug factor because there were lower scores under placebo than Dexedrine (63.4 versus 68.2).

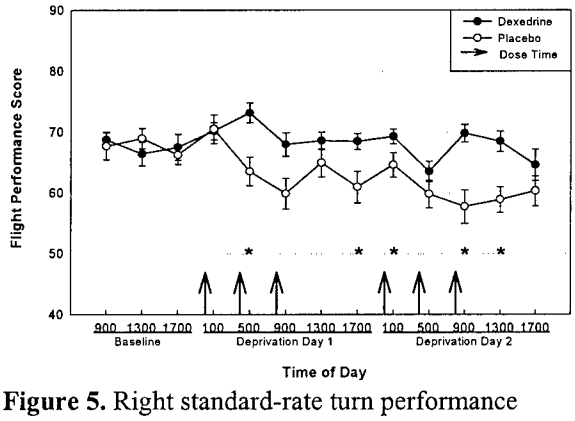

Figure 5. Right standard-rate turn performance

Left descending turn. There was a drug-by-session interaction because of no predrug differences at the 0900 and 1300 flights, but poorer performance at the end of the placebo baseline than the Dexedrine baseline ($p < .05$). Scores were then unaffected at 0100, but afterwards, scores under placebo were lower than under Dexedrine at 0500 ($p < .05$), marginally lower at 0900 ($p = .0653$), and significantly lower at 1300 ($p < .05$) on the first deprivation day. Similar differences ($p < .05$) were seen at 0500 and 0900 the next day (see figure 6).

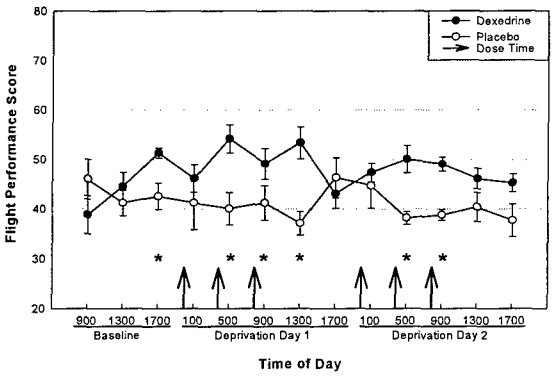

Figure 6. Left descending turn performance

Waking EEG data

Absolute power from the EEG were analyzed with ANOVAs consisting of three factors: drug (placebo versus Dexedrine), session (1015, 1415, and 1815 on baseline day; and 0215, 0615, 1015, 1415, and 1815 on deprivation days 1 and 2), and eyes (eyes open/eyes closed).

Delta activity. There were drug-by-session effects at F_z, C_z, and P_z due to more delta under placebo than Dexedrine at 0615 and 1415 on the first deprivation day, and at 0215, 1015, and 1415 on the second deprivation day. Drug main effects at F_z, C_z, and P_z were attributable to higher delta under placebo than Dexedrine. The drug-by-session effects at C_z are shown in figure 7.

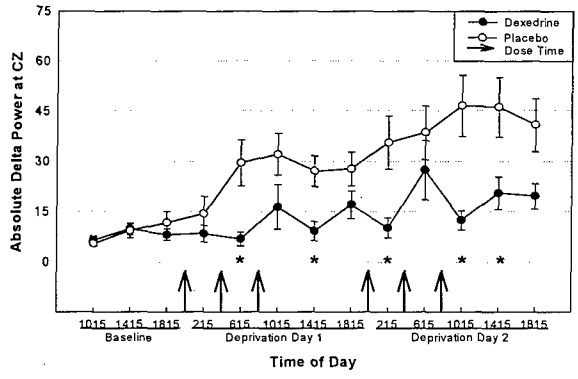

Figure 7. Absolute delta power at C_z

Theta activity. Drug-by-session interactions at F_z, C_z, and P_z were due to increased theta under placebo compared to Dexedrine at 0615 and 1015 on the first deprivation day and at 0215 and 1415 on the second deprivation day ($p<.05$). There was a difference on the first deprivation day between the drug conditions at 1415 for F_z ($p<.05$), a marginally-significant difference at 1415 for P_z ($p=.0617$), and no difference at 1415 for C_z. On the second deprivation day, there was a difference at 1015 for F_z ($p<.05$), a marginally-significant difference for C_z ($p=.0608$), and no difference for P_z. There was a difference at 1815 for both F_z and P_z. Drug main effects were due to more theta under placebo than Dexedrine. The drug-by-session effects at C_z are shown in figure 8.

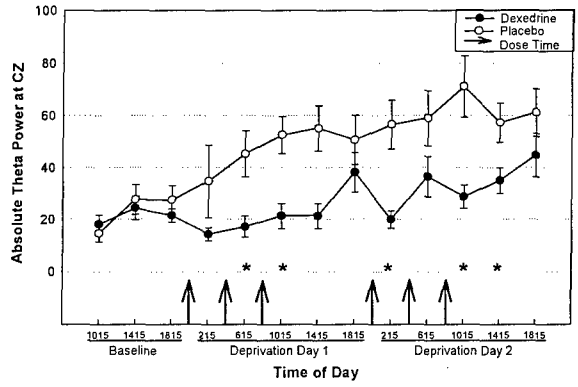

Figure 8. Absolute theta power at C_z

Alpha activity. There was a drug-by-session interaction at F_z due to higher alpha under placebo than Dexedrine at 1415 on the baseline day (predrug), but lower alpha under placebo than Dexedrine at 0615 on the first deprivation day ($p<.05$).

Beta activity. A drug-by-session interaction at P_z was because of less beta under placebo than Dexedrine at 1815 on the first deprivation day and more beta under placebo than Dexedrine at the same time on the second deprivation day ($p<.05$).

POMS

Scores under placebo and Dexedrine at the 4 baseline sessions (1120, 1520, 1920, and 2340) and 12 deprivation sessions (0320, 0720, 1120, 1520, 1920, and 2340 on deprivation days 1 and 2) were analyzed with ANOVAs for drug and session.

Tension-anxiety and depression-dejection scales. There was only a session main effect on both of these scales. No drug-related effects occurred.

Anger-hostility scale. There was a drug main effect ($F(1,4)=9.76$, $p=.0354$) on anger-hostility scores, which reflect anger and antipathy towards others. Scores were slightly higher under placebo than Dexedrine (0.4 and 0.6, respectively).

Vigor-activity scale. A drug-by-session interaction was due to the absence of predrug differences, followed by lower vigor scores under placebo than Dexedrine at 0320, 0720, 1120, 1520, and 2340 on the first deprivation day and at 0320 on the second day ($p<.05$). There were no differences between the two after 0320 (see figure 9). A drug main effect was due to lower vigor ratings under placebo compared to Dexedrine (13.9 versus 19.6).

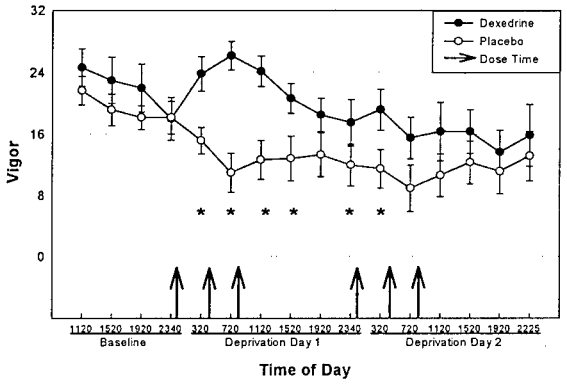

Figure 9. POMS vigor-activity scale

Fatigue-inertia scale. There was an interaction between drug and session and a main effect on the drug factor. The interaction resulted from the absence of baseline differences, followed by higher levels of fatigue under placebo than Dexedrine at 0720, 1120, and 1520 on the first deprivation day ($p<.05$). Fatigue tended to be higher under placebo than Dexedrine at 2340 ($p=.0557$). There were no differences at later times (see figure 10). The drug main effect was due to more fatigue under placebo than Dexedrine (6.5 versus 3.0).

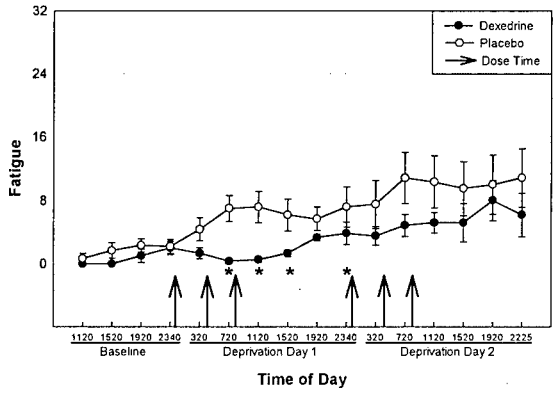

Figure 10. POMS fatigue-inertia scale

Confusion-bewilderment scale. There was a drug-by-session interaction and a drug main effect. The interaction was attributable to the lack of baseline differences, followed by higher confusion scores under placebo than Dexedrine at 1120, 1520, 1920, and 2340 on the first deprivation day and at 0720 and 1920 on the second deprivation day ($p\leq .05$) (see figure 11). The drug main effect was due to increased confusion under placebo relative to Dexedrine (4.1 versus 2.0).

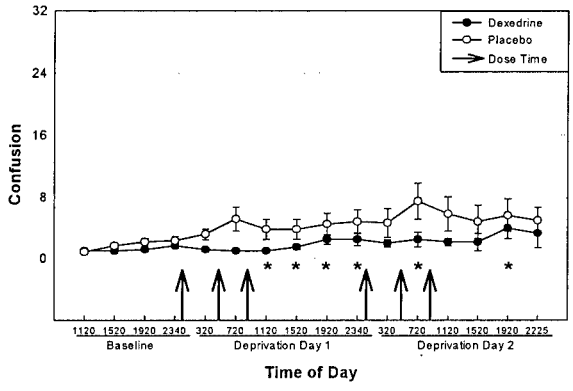

Figure 11. POMS confusion-bewilderment scale

Polysomnographic data

Data from the baseline night and the first recovery nights following Dexedrine and placebo were analyzed with a one-way ANOVA. There were differences among the days for sleep onset because of delayed sleep on baseline compared to either recovery night (the means for baseline, Dexedrine, and placebo were 8.9, 2.9, and 2.9 minutes). Sleep efficiency was higher during both recovery nights than during baseline, and higher after placebo than Dexedrine ($p<.05$). The means for baseline, Dexedrine, and placebo were 88.3, 94.1, and 96.4 percent, respectively.

The percentages of time spent in stage 1, stage 3, stage 4, and stage REM differed across the nights. There was more stage 1 during baseline than either of the recovery nights and more stage 1 during the Dexedrine recovery night than during the placebo recovery night. There was less stage 3 during baseline than the Dexedrine recovery night and more stage 3 during the Dexedrine than placebo recovery; however, the baseline and placebo recovery nights were equivalent. There was less stage 4 during baseline than the Dexedrine recovery night, but no differences elsewhere. There was more REM during the placebo than the Dexedrine recovery night, but no differences elsewhere (see figure12). REM latency was different

across the nights with the longest latency following Dexedrine. Latency also was longer during baseline than after placebo (the means for baseline, Dexedrine, and placebo were 70.6, 142.1, 37.7 minutes).

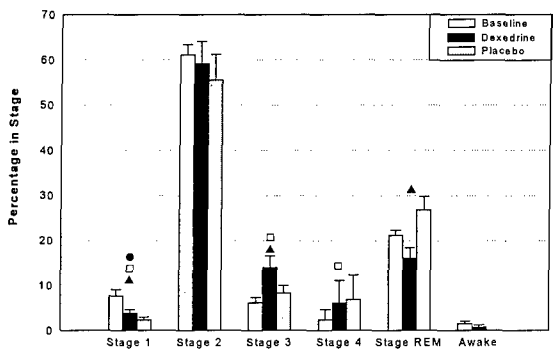

Figure 12. Sleep stage percentages (The filled circle denotes a difference between the baseline night and the placebo recovery night, the square denotes a difference between the baseline night and the Dexedrine recovery night, and the filled triangle denotes a difference between the Dexedrine and placebo recovery nights).

Discussion

This investigation extended earlier findings regarding the efficacy of Dexedrine for maintaining the performance and alertness of sleep-deprived pilots. Prophylactic administration of repeated 10 mg doses previously had been shown to attenuate the impact of sleep loss during 40 hours of wakefulness. This was particularly the case after 20 to 29 hours (0300-1200) and beyond. The present study examined whether Dexedrine would sustain performance and alertness for up to 64 hours without sleep. Flight performance was maintained by Dexedrine for up to 58 hours (the last flight of the investigation) while performance under placebo deteriorated. Dexedrine exerted the most reliable effects at 0500 and 0900 on both deprivation days. These are the times when alertness suffered the most (especially under placebo), probably due to the circadian temperature trough between 0400 and 1100. However, Dexedrine was often better than placebo at later times as well. Dexedrine attenuated performance reductions on two of the six maneuvers as early as 0100 on the second deprivation day (after 42 hours awake), on four of the maneuvers at 0500 (after 46 hours awake), on four of the maneuvers at 1300 (after 54 hours awake), and on one maneuver at 1700 (after 58 hours awake). Generally, performance under placebo declined from the first 0500 flight through the last 1700 flight. Dexedrine prevented this on all but one maneuver. These findings with 10-mg doses extend those of Pigeau et al.[20] who reported widely spaced 20-mg doses attenuated initial performance declines and recovered already-degraded performance.

Physiological indices of fatigue/alertness

A slowing of CNS activity as a function of sleep loss (especially under placebo) no doubt accounted for many of the performance decrements. Although there were numerous deprivation-related changes in the brain activity of subjects, the most pronounced were in the delta and theta bands. Slow-wave EEG activity has been found to increase as a function of sleepiness and fatigue,[19] and increased delta and theta activity are associated with performance decrements on vigilance tasks.[3] Also, increased theta power is associated with reduced speed of responding to incoming stimuli.[17] In the present case, delta and theta were elevated under placebo relative to Dexedrine as early as after 23 hours of wakefulness. Under placebo, slow-wave EEG continued to increase throughout 55 hours (and sometimes 59 hours) of deprivation. Under Dexedrine, the accentuation either was absent or the slope was noticeably reduced. Theta (and often delta) elevations under placebo relative to Dexedrine probably accounted for the inferior flight control which was most apparent after 22-26 and 42-46 hours without sleep.

Self-reported mood and sleepiness

Deteriorations in mood and alertness throughout deprivation occurred regardless of whether drug or placebo was administered. However, vigor decayed more sharply and fatigue and confusion increased more rapidly as a function of sleep loss under placebo than under Dexedrine. Drug-related differences appeared early in the deprivation cycle under placebo (after 20 hours without sleep), but under Dexedrine, ratings actually improved at this time. The decline under placebo continued for at least another 4 hours, at which time there was a leveling off, followed by a slight recovery in the afternoon of the first day. During the second deprivation day, a similar trend was observed in which vigor declined most notably after 48 hours of continuous wakefulness under placebo, whereas ratings again improved under Dexedrine. Despite the inability of Dexedrine to fully arrest *perceived* decrements in vigor, *actual* performance remained relatively constant throughout deprivation, similar to a report by Newhouse et al.[16] The absence of parallel declines in both data sets suggests subjects were aware of their

impairment, but this did not detract from their actual response capacity.

Recovery sleep

Differences between baseline and recovery nights occurred regardless of whether subjects received Dexedrine or placebo prior to recovery sleep. Sleep onset was faster and sleep quality was better after both deprivation periods than on the baseline night due to substantial sleep pressure following sleep loss. Also, there were differences in recovery sleep related to whether subjects received Dexedrine or placebo during the deprivation period. In the Dexedrine condition, subjects had received 30 mg of drug on the first day, and before this was eliminated (Dexedrine has an average half-life of 10.25 hours), the next series began. Thus, by bedtime on the second day (15 hours after the final dose), there were probably 10-15 mg of Dexedrine remaining in the participants' systems. This produced lighter sleep as well as disturbed REM sleep.

It is difficult to know whether lighter sleep after Dexedrine affected recovery since next-day performance couldn't be reliably compared (there would have been only three subjects per group); however, the size of the effects suggests that any problems would be minimal. The impact of altered REM sleep during recovery is difficult to estimate since the function of REM sleep is not fully understood.[13, 10] If it consolidates memory and/or restores mental resources, repeated use of Dexedrine might lead to progressive deterioration of higher-level thought processes. However, it seems unlikely that this would rapidly manifest itself as long as 1 night of recovery sleep is allowed after 40-hours of continuous wakefulness,[5] and 2 nights of sleep are permitted after 64-hours.

Summary and conclusions

Flight performance, physiological arousal, and mood were sustained by Dexedrine throughout 64 hours of continuous wakefulness. Dexedrine's effects were most apparent, from approximately 0300 until 1200 on both days. Generally there were no clinically-significant side effects attributable to Dexedrine; however, one subject evidenced increased diastolic blood pressure that would have been cause for concern had it not decreased when he was retested in a prone position. One subject became excitable and talkative under Dexedrine, but his flight performance was better than it was under placebo.

Although there is no substitute for sleep, Dexedrine should be considered an appropriate countermeasure for use in operational environments where short-term (i.e., 64 hours) sleep deprivation is unavoidable and a high level of performance is required. However, whether Dexedrine could preserve performance in longer periods of sleep deprivation is unclear. A follow-on study involving 112 hours of deprivation is recommended.

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The opinions, interpretations, conclusions, and recommendations are those of the authors are not necessarily endorsed by the U.S. Army and/or the Department of Defense.

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